DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE MEETING

Advice on CFSAN'S Draft Report: Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

Friday, July 15, 2005

8:00A.M. to 9:45 A.M.

Greenbelt Marriott
6400 Ivy Lane
Grand Ballroom

Greenbelt, Maryland 20770

PARTICIPANTS

FOOD ADVISORY COMMITTEE STANDING MEMBERS:

Richard A. Durst, Ph.D. - Acting Chairman
Jeffrey A. Barach, Ph.D. (Industry Representative)
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Dennis Gonsalves, Ph.D., M.S.
Jean M. Halloran (Consumer Representative)
Douglas C. Heimburger, M.D., M.S.
Margaret C. McBride, M.D.
Mark Nelson, Ph.D. (Industry Representative)
Carol I. Waslien Ghazaii, Ph.D., R.D.

TEMPORARY VOTING MEMBERS:

Petr Bocek, M.D., Ph.D.
Margaret Briley, Ph.D., R.D.
Erica Brittain, Ph.D.
Ciaran P. Kelly, M.D.
Soheila June Maleki, Ph.D.
David O. Oryang
Marc D. Silverstein, M.D.
Suzanne Teuber, M.D.

FOOD AND DRUG ADMINISTRATION:

Robert E. Brackett, Ph.D. - Director
Food and Drug Administration, CFSAN

Catherine Copp, J.D. - Senior Policy Advisor
Food and Drug Administration, CFSAN

Steven M. Gendel, Ph.D. - Senior Scientist
Food and Drug Administration
National Center for Food Safety and Technology

Rhonda Kane, M.S., R.D. - Consumer Officer
Food and Drug Administration, CFSAN

P A R T I C I P A N T S (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

Michael M. Landa, J.D.
Deputy Director for Regulatory Affairs
Food and Drug Administration, CFSAN

Stefano Luccioli, M.D. - Senior Medical Advisor
Food and Drug Administration, CFSAN

Marcia Moore, Food Advisory Committee, Executive Secretary

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PROCEEDINGS

Call to Order and Welcome and Introductions

CHAIRMAN DURST: I would like to convene the final session of our committee meeting this morning. Let me begin by again stating that there are the conflict of interest statements over on the side table for anyone who wants to avail themselves of that information.

Also, rather than waiting for the very last minute to thank the various people who made this meeting possible, I just wanted to thank Marcia and her staff for taking such good care of us and providing all of the information we needed to have a successful meeting.

I also want to thank the USDA Graduate School for providing support and the Marriott Hotel of course for providing very nice facilities to do this work.

In addition, I would also like to take the opportunity to introduce Dr. Robert Brackett, who is the director of the Center for Food Safety & Applied Nutrition, who was able to join us for a

couple of hours this morning.

Bob, if you want to say a few words?

Welcome

DR. BRACKETT: Thanks, Dick.

The only thing I wanted to say -- I know you are all in a hurry to get things done and get to your airplanes this morning, too -- I had hoped to be here for more of the meeting this week, but I have been stuck at other meetings. However, I do want to let you know how supportive I am of the advisory committee structure.

I served on this Committee a number of years ago, and I know that it is a big time commitment and there is a lot of studying to be done, a lot of discussion, so FDA really does appreciate your participation and your expertise.

This is something I think that has more value added to it for us than we could have gotten individually and breadth of knowledge, and so I do thank you also.

I would also like to extend that I hope that you will continue. I hope that you will tell

your colleagues, when they are asked to serve on this Committee, that this is something that they really do provide a great service to the country and to the regulated industry that we deal with.

With that I will let you conclude your meeting this morning, and thank you for being here.

CHAIRMAN DURST: Thank you, Bob.

Yes?

DR. TEUBER: I found out, in my rush to get over here, one page is still on the printer at the concierge desk. If there is a Marriott staff person who could pick up the third page from the printer, behind the concierge desk, that would be fantastic. It is a printout of just a draft of our summary here.

Committee's Discussion and Response to FDA's Charge and Questions

CHAIRMAN DURST: Okay. Thanks, Suzanne.

I assume I don't have to read the charge again, since we know what we are here for. We have been dealing with this for two days now.

To remind you, we don't have to come up

with, certainly, a vote. We don't even have to come up with a consensus. What we want to do is provide the FDA with some guidance and recommendations on the draft report that we have been discussing the past two days.

I have asked several members of the Committee to try to summarize the remarks or comments and discussion that has gone on for the past two days.

I have asked Marc and Suzanne to summarize the food allergens part of our first day of discussions and Ciaran to summarize the celiac disease, the gluten portion.

After their presentations, we will open it for discussion to make any comments agreeing, disagreeing or just filling in some blanks that they think are important.

Then, after that part, we will go back and deal with the general questions that are on the charge sheet. That I think should go fairly quickly after we have agreed on some of the other items that we are going to discuss.

Even though it is out of order, maybe we will start with Dr. Kelly with the discussion of gluten, since we are waiting for the page on the food allergens.

Ciaran.

DR. KELLY: Sure. Ciaran Kelly here. Should I read the questions, or just go straight to the answers?

DR. TEUBER: Yes, please.

DR. KELLY: So the first question is regarding gluten and celiac disease. Is there a distinct subpopulation of individuals with celiac disease that have an increased sensitivity to gluten?

If so, for the safety-assessment-based approach, is the proposed uncertainty factor for intraspecies differences tenfold sufficient to ensure that exposure levels will be below the level of sensitivity for this highly sensitive subpopulation? If this uncertainty factor tenfold is not sufficient, what uncertainty factor should be used?

Sensitivity to gluten does vary from one individual to another at the level of clinical symptoms. However, symptoms of celiac disease do not parallel small intestinal mucosal injury as assessed by small bowel biopsy histology, which is the widely accepted quantitative method of assessing gluten-induced injury in celiac disease.

There are insufficient available data to state with any certainty or to what extent individual variations influence the intestinal mucosal changes of celiac disease in response to specific levels of gluten exposure. Thus, it is not possible currently to assign a reliable uncertainty factor for intraspecies differences in gluten sensitivity.

The Committee is uncertain as to whether or not it is appropriate to apply an uncertainty factor for intraspecies variation in the immunological responses to gluten and celiac disease that is based on the standards normally used for toxicology studies.

The magnitude of the uncertainty factor

will also be influenced by the level of individual variation observed in the studies used to determine that threshold. The choice of an uncertainty factor for a dietary gluten threshold will also be influenced by the ability to measure the gluten content of foods.

It is likely that the gluten threshold together with a modest or moderate uncertainty factor will lie close to the lower limits of performance of the currently available assays and this may, at least in the short-term, dictate the measurable threshold.

CHAIRMAN DURST: Okay. Does anyone have any comments or discussion on Ciaran's presentation on that question?

(No response.)

CHAIRMAN DURST: I guess most people are in agreement on that. Very good.

DR. KELLY: The second question: Is it scientifically sound to use data from short-term clinical studies that evaluate the effects of acute gluten exposure to predict the effects of long-term

gluten exposure in gluten-sensitive individuals?

What uncertainty factor is appropriate for thresholds developed using available short-term clinical studies in order to prevent adverse effects associated with chronic effects.

Data from acute challenge studies that examine intestinal mucosal changes in response to brief exposure to gluten peptides of several hours or days' duration are not widely accepted as a valid method to determine a gluten threshold.

However, there is general acceptance in the medical and scientific community of studies that examine mucosal responses to several weeks or months of exposure.

If threshold values are based on challenge studies that examine in a quantitative fashion the mucosal responses to several weeks or months of gluten exposure, then the uncertainty factor needed for chronic exposure will be minimal.

Additional valuable data are also available from other countries, particularly in Europe, that have many years of experience with

enacted threshold values. Those data may also reduce concerns regarding the need for an increased uncertainty factor based on prolonged duration of gluten exposure.

Since a determination of threshold values must be made in the context of incomplete and evolving medical and scientific knowledge, the Committee endorses the Working Group's finding that any threshold value that may be set for gluten must be continually reevaluated, and, if new information warrants, be adjusted.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Okay. I guess I just want to summarize. I have a slightly different perspective on this. I don't think my bottom line is really that different. But from a statistical perspective, it is hard for me to know that a three-month exposure study would tell me everything about the cumulative, chronic exposure; so, I would be a little more uncertain than some of the people on the Committee were yesterday.

However, that concern is softened by the

fact that we do have the observational data that seem to suggest a similar effect; so, I think my bottom line is probably pretty similar to yours, although maybe a little more uncertainty.

CHAIRMAN DURST: Thank you.

Anyone else?

David.

MR. ORYANG: Yes. David Oryang. I think your concern is well-taken. I think the key thing here is to remember that if it is clearly documented or at least if evidence documents how we came about determining that safety factor, that is the key thing.

As long as it is documented and transparent, then people will be able to comment on it or provide better information to determine better safety factors.

The clear thing is that there should be a good documentation of how the safety factor came about. I think that is the key so that experts and others who review it can then give better comments or suggestions on how to improve it, if it doesn't

seem right.

CHAIRMAN DURST: Okay. Thank you. Any other comments?

(No response.)

CHAIRMAN DURST: I guess we can proceed. Ciaran.

DR. KELLY: The third question: Are current data sufficient to conclude that a portion of celiac patients are or are not also susceptible to gluten proteins naturally occurring in oats, i.e., prolamines and glutelins, if not, what additional data is needed to draw such a conclusion?

Published data indicate that the majority of individuals with celiac disease do not demonstrate significant symptoms or signs in response to oats.

A meta-analysis of these published studies may serve to strengthen this conclusion. There are a very small number of documented cases where individuals with celiac disease showed an immune-based response to oat proteins.

However, the low frequency of these reports indicate that the overall approach to setting a threshold for gluten should not be unduly influenced by the relatively minor concern regarding oat-sensitivity. Of greater concern is the issue of cross-contact leading to low-level contamination of foodstuffs with the known toxic gluten proteins.

CHAIRMAN DURST: Thank you. Comments?

(No response.)

CHAIRMAN DURST: Good. Thank you.

DR. MALEKI: Well, I have one.

CHAIRMAN DURST: Oh, I'm sorry.

DR. MALEKI: Soheila Maleki. Just one comment. The other concern that I think wasn't mentioned is that limiting the food choices of the people that are celiacs is probably self-included. I just wanted to mention that.

CHAIRMAN DURST: Okay.

DR. KELLY: Then, the fourth question: Are all individuals with celiac disease equally at

risk for developing consequences -- for example, cancer -- and increased mortality from the long-term ingestion of gluten?

Are current data from clinical studies or from individuals with celiac disease on a gluten-restricted diet sufficient to estimate the magnitude of any increased risk of mortality for these individuals?

The outcomes of celiac disease vary widely, from lifelong silent disease to fatal malignancy. However, at this time the only identified risk factor for bad outcomes, including death from malignancy, is poor or absent compliance with a gluten-free diet.

Prolonged, strict adherence to a gluten-free diet clearly reduces the risk for gastrointestinal symptoms and nutritional deficiency states such as anemia and osteoporosis and celiac disease.

The available data, though limited and imperfect, indicate that prolonged, strict adherence to a gluten-free diet also reduces the

risk for malignancy.

Thus, instituting measures that facilitate compliance with a strictly gluten-free diet are the only known approach to reduce the overall risks associated with celiac disease.

Comments? Questions?

(No response.)

CHAIRMAN DURST: Good job, keep going.

(Laughter.)

DR. KELLY: Question five: Is evidence of minimal intestinal pathological change, for example, increased intraepithelial lymphocytes following a gluten challenge, an appropriate symptom upon which to base a LOAEL for long-term consequences?

Are other biomarkers such as clinical symptoms or more severe intestinal pathological changes more accurate predictors of long-term consequences?

Yes, the characteristic intestinal pathological changes of celiac disease, for example, reduced villus-to-crypt ratio and

increased intraepithelial lymphocyte counts constitute the widely accepted gold standard for celiac disease diagnosis.

These changes are also widely accepted as the gold standard method for evaluating disease activity following a gluten challenge. Other disease markers such as symptoms, antigliadin antibody, tissue transglutaminase or endomysial antibody levels, or measures of mucosal permeability are considered of secondary value in quantifying disease activity.

CHAIRMAN DURST: Comments?

(No response.)

CHAIRMAN DURST: Very good, Ciaran. Thank you very much.

I don't know, as far as what is allowed, may I ask the Threshold Working Group if they have any additional questions or clarifications they need on those points?

(No response.)

CHAIRMAN DURST: Well, we are moving, then.

Okay. Suzanne and Marc, are you ready to present to your comments?

DR. TEUBER: Okay. Suzanne Teuber here. For this discussion, it turned out as we went through the questions that there were actually some that we did not specifically address in the Committee discussion, and so there will be discussion that is needed this morning in order to answer the charge

For the first question: are there distinct subpopulations of highly sensitive individuals within the allergic population for each of the major food allergens?

We know that there are huge differences in threshold doses and a continuum of reaction severity upon ingestion from mild to life-threatening for each of the major food allergens.

However, it is not possible at this time to identify "distinct" subpopulations of individuals by clinical criteria, previous frequency or severity of allergic reactions, or

threshold responses on a double-blind, placebo-controlled, food challenge within populations sensitive to specific allergens for which thresholds or uncertainty factors can be identified. That is number one.

Any thoughts on that one?

(No response.)

DR. TEUBER: Okay. Then, number two, I will hand over to Marc here.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Yes, I just want to add one comment. In terms of all of these questions about the food allergies, from my statistical perspective, again, to me the first step here of when the Working Group actually is setting a threshold is to define what the precise goal of the threshold is; in terms of the sensitive population or the overall allergic population, what risk level is acceptable. I think that is the first step.

DR. SILVERSTEIN: Actually, these are additional comments under one, so why don't I continue with that.

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DR. TEUBER: Okay.

DR. SILVERSTEIN: The next part of the question of number one says: "If so, for the safety-assessment-based approach, how to propose uncertainty factors for intraspecies differences 10-fold, under severity of responses for this sensitive population tenfold, sufficient to ensure exposure levels will be below the level of sensitivity for the highly sensitive populations?"

The uncertainty factor for sensitive populations is unknown when considering food allergy and immune response as compared to classic safety assessment and toxicology.

The selection of an uncertainty factor for allergens should be informed by the distribution of the NOAELs and the LOAELs using measures of the spread of data such as standard deviation, interquartile range or ranges.

If reproducible, subjective responses in patients with a history of life-threatening anaphylaxis are included in setting LOAELs and NOAELs, the uncertainty factor might be lower than

10.

The selection of thresholds for allergens should be informed by evidence of the thresholds of NOAELs and LOAELs. However, as we mentioned, bias due to exclusion of the most sensitive individuals who have experienced life-threatening allergic reactions, anaphylaxis, require caution in using currently available data.

All currently available published and unpublished data should be specifically assessed for potential selection, referral bias, and other factors that influence the individuals who are actually studied.

There is also uncertainty due to variation between individuals in a population and uncertainty due to variation within individuals over time. There are inadequate prospective studies performed with the goal of seeing if the objective response thresholds have changed in patients with persistent food allergy, except in those who are expected to have developed a tolerance.

A highly sensitive individual might have a

lower or higher LOAEL compared to baseline depending on such factors as: the season of year; theoretically, increased histamine release potential based on activity of conditions such as allergic rhinitis and asthma, which might be seasonal; status of an atopic dermatitis; the time of day; stability of the patient's underlying asthma; ingestion of other factors such as alcohol, exercise, pre- or post-ingestion, matrix effects of food, processing the food, progression of the degree of their allergy based on IgE target, epitope diversification, antibody increases, and other variables which are known to individuals in the field.

The next part of the question: If these uncertainty factors are not sufficient, what uncertainty factors should be used for the safety-assessment-based approach?

A concrete number was not offered by the Committee. The Committee noted that the uncertainty levels of tenfold or a hundredfold had been used in biomedical toxicology. IgE-mediated

allergic reactions essentially are amplifiers. They amplify reactions to minute amounts of allergens.

So, the application of uncertainty factors to thresholds on the double-blind, placebo-controlled, food challenge may not be sufficiently large to handle this variation of amplification of an allergic response.

DR. TEUBER: That was the entirety of number one.

CHAIRMAN DURST: I beg your pardon?

DR. TEUBER: It was the entirety of number one; it is put out in sections.

CHAIRMAN DURST: It is open for discussion.

Erica.

DR. BRITTAIN: I agree with all that. I just want to add one point that as an alternative to the uncertainty factors another strategy is the modeling approach that we heard the speaker talk about. I think that is a really promising approach to assessing risk.

However, even with that, you would need to make sure that you have data that represents the entire target population. I don't know that really is available at this point.

CHAIRMAN DURST: Any other discussion? Mark.

DR. NELSON: Yes, this is Mark Nelson. I agree with your synopsis as well, and I think you have captured a lot of hours of struggle, but one thing I wanted to clarify. I do agree that the uncertainty factors should be based on the range, the largest range possible, of the sensitive individuals. But I heard, and correct me if I'm wrong, that some of the studies did in fact include some extremely sensitive individuals.

DR. TEUBER: Yes, some did. And then we also had the situation where in some studies the extremely sensitive people challenges were stopped at subjective which -- well, that was in some of the hazelnut study.

But for the Hourihane study, for instance, they did go on. It was a twenty-fold difference in

one patient, a fifty-fold difference in the other between a subjective response and an objective response.

DR. NELSON: Right.

DR. TEUBER: We definitely want things to be based on objective, when possible, but I am concerned that in the threshold studies that are going to be done by the consensus protocol there is still room for a physician or a patient to decide to stop.

I mean, they have the ability and informed consent procedures to stop at any time, and so if they are recruiting the most sensitive, we may have folks who back out before an objective response or where the physician decides, "Ah, you know, they're complaining of throat swelling, and I can't see anything, but I'm hesitant to go on."

There, that data of the subjective I think should be used. It doesn't carry the weight of an objective NOAEL but certainly could be used to help estimate an uncertainty factor.

DR. NELSON: Yes. I don't mean at all to

imply that people should be forced to participate in these studies or continue on, if subjectively they have lost comfort. What I wanted to point out was that I understood that the database as it exists now, there are some studies that do have very sensitive individuals in them.

DR. SILVERSTEIN: I think this is one of the most difficult -- this is a discussion point not a summary point -- issues is assessing potential bias. There are of course in randomized-controlled trials a careful focus on eligibility an exclusion criteria.

In observational studies and in studies of diagnostic test assessment, the eligibility and exclusion criteria may or may not be as explicitly stated.

In any case, when a study does have well-stated eligibility and exclusion criteria, you often don't get a description of those people who are referred or screened and not studied. Because they are not studied, you usually have less information.

Because this is a serious life-threatening condition, because these studies were done at distinguished academic centers by individuals who have distinct experience, to appear in such a study often you need to be referred; and so the referral bias, we are often not able to assess it.

The strongest studies are those that we would call "population-based studies." Those would be the things you would want to look for. Oftentimes, that is not stated or it is only implicit in understanding that this study, as study subjects, the study subjects are often referred to as "the population," because we are making inferences about similar subjects. But the study subjects, because of referral, weren't truly representative of the population of allergic individuals.

That is the concern, and that is the challenge the FDA will have in evaluating this literature, but it needs to be looked at for all available literature.

CHAIRMAN DURST: Dick Durst. I would also

like to remind the Working Group that when they set these thresholds they also have to be cognizant of the analytical methods.

When you put on an uncertainty factor or a safety factor onto these thresholds, you have to be tempered by the knowledge of what analytical methods can do as far as verifying and making sure that foods comply to these thresholds. At the present state of the art I think there are some problems in this respect, so that this has to be taken into consideration.

DR. TEUBER: Suzanne Teuber. When you go through the back of the binder and look at the different foods and the sensitivity and actually for the objective, quantitative measurements of what can be done, if an uncertainty factor is applied that is too large, you will be below those levels. You end up then with the analytical method as the method of choice for some of these.

Additionally, if you consider, the Working Group should consider, that the serving size may be subject to discussion when you are determining how

many parts per million may be acceptable.

I guess I really need to retract that. It is just that based on clinical experience now so many patients go by that first subjective response in the mouth of having some tingling or some itching and have been able to stop -- I'm sure if Anne Munoz-Furlong were here she has thousands of stories of this; I have hundreds and hundreds.

So, the serving size where a person may notice a subjective response may be much smaller than the 100-gram serving size that may be used to calculate how many parts per million are going to be acceptable before a NOAEL with an appropriate uncertainty factor applied is reached.

CHAIRMAN DURST: David.

MR. ORYANG: Yes, David Oryang. Just adding, I think, yes, if a safety factor is derived in a science-based way, even if the sensitivity is much greater than the sensitivity of any of the test methods.

I think it should be transparently communicated, and then the decision will be made,

hopefully, at FDA as to how to resolve that, maybe through labeling and saying, well, it is clear that we don't have the methods to be able to detect that level, those parts per million that individuals are sensitive to.

I think the products could be labeled appropriately so that those at risk can make the choice whether or not to go ahead and take on that risk, but I don't think we can temper the science based on available methods, necessarily.

They are two different things: there are the safety issues and then how do we apply what we know. If there is no method of applying or detecting that level of sensitivity, then it needs to be transparently presented, I think, as opposed to altering the safety factor so that it is within a range of detectability.

CHAIRMAN DURST: Erica has a comment.

DR. BRITTAIN: Yes. This is touching on something that I tried to say yesterday, and I think I said it badly. Let me take one more chance to try to say it again. At some point the FDA will

be establishing a threshold for each allergen. I hope it will be a really safe and really conservative threshold.

Presumably, it will be above the level of detection. It means there will be this gray zone. Some products will fall in the gray zones between the level of detection and the threshold that was set.

I am wondering if there would be any value in being able to provide that information to the consumer that this product say something like "contains peanuts but below the allergenic level."

So, that mom who was here on Wednesday who said, "I don't want this threshold based on a statistical estimate, I want it based on fact," if she does not want to take any chance at all, she can see, "Oh, it's in that gray zone, and I don't want to take any chance."

Or, if someone has had experience in the past with reactions in that gray zone, then they may think they are the rare individual that cannot tolerate that level. I just wanted to throw that

out one more time.

CHAIRMAN DURST: Okay. Carol and then Soheila.

DR. WASLIEN: Well, one of the problems I see with the detection method is that we don't even know what the allergen is in a good number of cases, so having a good detection method may be detecting the wrong thing. It is that kind of problem with detection methods, too, that lead to the uncertainty factor.

DR. TEUBER: Suzanne Teuber. I actually disagree with that. Because if you have a method that is just aiming to detect the food, the proteins in the food that are allergens are going to track along with that measurement. Just as the measurements for gluten, the glutelin fraction will track along with the gliadin fraction is measured.

If all of our tests so far that are measuring the food given are based on total protein, it all seems to track together in a proportionate way. I think that is okay.

DR. WASLIEN: You don't see a case where protein would be separated and only one of the protein fractions would be included in the food and therefore safe?

DR. TEUBER: Well, yes, where you have casein used or alpha-lactoglobulin or whey as separate fractions.

DR. WASLIEN: Yes.

DR. TEUBER: There you do have a situation where the challenges that are done to determine the NOAELs and LOAELs have been with the whole protein. Actually, yes, I do see that as a potential problem, but the actual challenge dose that would elicit -- actually, yes, that is a good point, to think about the separation there.

DR. WASLIEN: Yes, particularly with milk protein.

DR. TEUBER: Yes.

CHAIRMAN DURST: Okay. Soheila and then Petr.

DR. MALEKI: Soheila Maleki. One comment for Erica. Well, currently the gray area exists

that is in "may contain" labeling. You are asking for something that already exists that the consumer is asking to take away. They want a more definitive response.

Second, there are analytical methods that can actually go down to measuring one molecule that is completely insignificant. Like I said, on this tablecloth here somebody can detect peanut or wheat, if they wanted to. You can go down to a molecular level, and washing won't get rid of it, that these people will not react to it.

There is a limit where allergic people will not react, and we do have the detection methods. What happens is we don't have the threshold data on the individuals.

Still, the consumer is asking for us to make some kind of decision on the best data available. I think that is something important to think about for the consumer, because that is why they are frustrated.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. Soheila pretty

much said what I wanted to say because that would apply to every product to assess their methods. One would be saying, okay, this product doesn't have, let's say, peanut at the allergenic threshold, yet it contains.

Here you go, you are restricting the consumer from basically anything. If you take the PCR, you are going to detect peanut everywhere. So I think it is absolutely impossible to apply that method. It has to be the allergenic threshold only. That is what the consumer wants, and that is going to make it clear. I absolutely agree with that. I don't think it is practical.

CHAIRMAN DURST: All right.

Mark.

DR. NELSON: Mark Nelson. Just to add to that from the practical standpoint of actually manufacturers labeling their products, we want to communicate clearly to the consumer. We don't want to add anymore gray to it, to the situation at all.

If a threshold can be established where the great majority of allergic individuals for a

particular allergen can be benefited by having that information, great, but we don't want to add to the gray.

CHAIRMAN DURST: Thank you.

Any further discussion on this question?

(No response.)

CHAIRMAN DURST: That was good. The next question.

DR. TEUBER: Number two: "Is the initial objective response seen in a clinical challenge study always an adverse effect that poses risk to human health?," is the first part of the question.

We said there was discussion of no, it is just uncomfortable, but then we kind of wrapped it up. We were making comments at the end, so here is what we ended up writing.

"Yes, if there is an objective response to a food in a double-blind, placebo-controlled study performed in a patient with IgE-mediated food allergy, this is an adverse effect that poses risk, albeit usually low.

"The findings from an objective response

in a double-blind, placebo-controlled, food challenge is sufficient for physicians to make recommendations that patients avoid specific foods and change lifestyle to avoid risk of life-threatening allergic responses. This is sufficient to conclude that objective responses are associated with allergic reactions that pose risk to human health."

Any comment on that part of the questions?

DR. MALEKI: Just one quick comment.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki, sorry. One quick comment that, yes, the subject of milk came up and I think when Petr and I were making comments on that we were thinking instead of just "to human health," we were thinking "life-threatening." That is why we said no. I agree, I believe that we can forward your response.

DR. TEUBER: Okay. Is it scientifically sound to use this response to determine a LOAEL in the absence of a NOAEL? We said no, reactions to the first dose, because that was implied in the

question, mean that the LOAEL could be just a trace lower or conceivably a thousand-fold lower. Such data are not useful in the decision-making process.

Then, the next part of the question: For the safety-assessment-based approach, is the proposed uncertainty factor of tenfold sufficient and appropriate to use in the absence of a NOAEL? We said no, such data should not be used at all.

Then, more on that question: If a clinical challenge study reports a subjective response of a lower dose than the dose that caused an objective response, should that observation be taken into account when determining the appropriate uncertainty factor?

Again, we have extremely limited data on subjective responses and the relationship to objective at this point. We said yes, if using a subjective response as the LOAEL, the uncertainty factor would be lower.

If using the objective response but subjective responses were also recorded, the uncertainty factor -- and this is a point that we

can discuss more today -- should probably extend to cover the dose at which the subjective response occurred and likely a bit further to account for the individual variation.

I might like to stop right there, because we did not actually specifically discuss that. As we were coming up with this, we wrote that. Again, our whole point is that we want the LOAELs to be based on objective data.

However, if you have subjective data as well, which the consensus protocol for threshold studies they are now going to be recording this subjective data, this might be very useful in judging what these uncertainty factors should be. I had put here that the factor should actually extend a bit below that. That was without any discussion yesterday.

How do you all feel about that? Again, this is just our recommendation.

CHAIRMAN DURST: Carol.

DR. WASLIEN: Hi, Carol Waslien. Since we don't know the individual factors that would

influence the subjective or objective reactions, I assume that we have to include that.

I would hope that we would accumulate data that says this is the kind of range within an individual that you might see, because that makes it exceedingly low in a sense or the lower limit. Over time, I would think that kind of data should be accumulated in trials.

CHAIRMAN DURST: Petr.

DR. BOCEK: Well, we didn't discuss it originally, but I absolutely agree with that. In practice, imagine you give a patient in a double-blind challenge study 100 micrograms of peanut, and they say, "I'm itching all over. My mouth is tingling. I don't feel well."

You go on and they develop hives only at 100 milligrams. There is absolutely no way I will say that 10 milligram is the norm, because they had subjective symptoms which to me are significant at 100 micrograms. I certainly agree with that approach.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: I would like to make a comment and an observation. In our understanding the drugs, we have had tremendous benefits by improved methodology that have been developed by investigators, epidemiologists, and statisticians in response to regulatory requirements that were developed and industry was focused on because of a need to develop drugs to be marketed.

It seems to me that in the setting of thresholds for allergens there is an opportunity here to specify a set of potential biases, a set of potential confounding factors that the leading investigators in the allergic diseases would use in establishing these consensus protocols for double-blind, placebo-controlled, food challenges.

If, for example, biases such as referral bias, selection bias, disease-spectrum bias, verification bias were judged to be important factors.

A set of standards for performing these studies could include reporting this information. Journal editors have also been influential in

improving the quality of studies by saying, "As a characteristic for publication, we would like you to meet these criteria."

If there were a set of confounding factors -- time of day, season, exercise, concurrent medications -- that are thought to be important by clinicians, by allergists, if those factors were specified as factors that should be reported in the collection of data, then as we go to making judgments about policy and regulations, we would have a more uniform and higher quality data to base those regulations.

If we think back about the way in which our knowledge of clinical trials has benefited by the need to have well-designed Phase I, Phase II, Phase III clinical trials, I think we are at an analogous point here.

These factors that we have, these potential sources of error and the potential incomplete data, I think could be used by those on the cutting-edge in doing these studies or designing these studies, so that as these studies

are conducted within one, two, three years we would have a body of data to make better judgments about the setting of thresholds. I think there is a very important opportunity here to influence the type of data that will be available in a couple of years.

CHAIRMAN DURST: Suzanne.

DR. TEUBER: A note to file, this would be an excellent RFA. Again, these studies are extremely expensive, and so the only ones that are underway right now or being planned are those being sponsored by industry, graciously, to help determine these thresholds. This is an excellent opportunity for us, as a Committee, to have in our minutes the need for more funding for this.

CHAIRMAN DURST: Jean.

MS. HALLORAN: It does seem like, following up on this, one of the critical questions is the relationship of subjective responses to objective responses. I don't know whether it has been studied so far how well these correlate or whether that is something that needs further study.

However, if in placebo-controlled,

double-blind studies a subjective response is a very good indicator of a subsequent objective response, then that would lend more validity to using the subjective responses as a factor in determining a threshold.

I was wondering if anybody knows whether that kind of correlation has been done up to this point; and if not, whether perhaps we might want to recommend research in this area?

DR. TEUBER: Suzanne Teuber. That actually is being incorporated into the current consensus protocol for threshold studies, that subjective responses will be recorded carefully, and then the goal is to proceed to an objective. This will allow us to have data on how those are related in a wider range of patients.

Because right now, there are only a few reports of proceeding on to an objective response after initially having a subjective one, I should also note, a subjective response verified by repeat challenge with negative placebo. It will come.

CHAIRMAN DURST: Any further discussion on

question two?

DR. TEUBER: Well, actually we have more on question two. That was just one little subsection there.

(Laughter.)

DR. TEUBER: Suzanne Teuber, I should say.

CHAIRMAN DURST: I thought we went through these.

DR. TEUBER: Oh, actually, no, you're right. That was basically it, but we have one little bit more that we wanted to add to this discussion of number two. We wanted to note again this recruitment problem.

Of note, recruitment of the highly sensitive subpopulations to threshold studies may be enhanced by recording subjective reactions that are reproducible to the active dose but negative to the placebo, two challenges of each, with an option of stopping at that dose.

In threshold studies, highly sensitive patients may or may not be willing to proceed to an objective response or the physician may not be

comfortable proceeding.

There is acknowledged controversy that is appropriate about the applicability of LOAELs that are subjective. Objective responses are preferred, with the concern that it be demonstrated in studies that extremely sensitive subjects have been willing to participate in, otherwise an uncertainty factor greater than 10 may be needed because we just don't have enough data.

Again, we wanted to note the previous comments that Mark had made about using a range of threshold values in determining the uncertainty factor. We actually raised these points in our discussion here again.

Then, proceeding on to number three: In the absence of specific data that would allow thresholds to be established for each of the major food allergens, is it scientifically sound to use the threshold established for a single food allergen -- for example, peanuts -- as the threshold for all major food allergens?

We really did not discuss this much

further. I think it could use a little bit more discussion. I said no, it appears from the available data that soy thresholds may be higher. Such labeling would then restrict diets unnecessarily as well as pose hardships to industry.

We really didn't discuss the fact that for other allergens we don't have much data or adequate data, and it might be reasonable to use the most stringent one until other data are available.

Any thoughts on this?

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I mean, that sounds good, just as long as you really are totally competent about what is the most stringent factors.

CHAIRMAN DURST: Carol.

DR. WASLIEN: Well, I think there are a good number of tree nuts, for example, that we have limited data on. Hazelnuts, yes; but other tree nuts, we don't have the data on. Other allergens, the other 200 that aren't part of the 7, we have to use something in their place.

Perhaps, until those ranges become more clearly established, we are safer at using a peanut allergen that is the most likely to show a response for those foods until they are proven otherwise, sort of guilty until proven innocent almost.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. It seems to me that a parent making a decision about food exposure for a child, a physician making a decision to recommend diet for a patient and an agency making a policy recommendation for consumers and industry, all are faced with difficult decisions.

The decision threshold and the potential decision you might make might be weighed not only by the likelihood of making a correct or incorrect decision, but the consequences of making a correct or incorrect decision.

Obviously, a parent making a decision for a child, a physician making a decision for a patient, and an agency making a decision for a population and industry all have different

thresholds in terms of the value of a false-positive or a true-positive recommendation to avoid or not avoid, or to change diet or not change diet, or to label or not label a specific level.

I do think that we are, in some sense, changing our perspective. We are putting on our hats or our roles as parents and individuals. We are putting on our judgments as clinicians or health care providers, and we are putting on our roles as policymakers.

I actually think we should be cautious in making judgments about how sensitive or specific our thresholds would be for a decision about our children, our decisions about our parents, and our decisions about our public population.

I am not sure that I would want -- in fact, let me phrase it positively -- I would not be comfortable making a decision to be very conservative or very liberal, if you will, high or low, highly sensitive, or specific when I shift my domain from that what I would do for my child to that what I might do for my patient or that what I

might do for an agency's decision.

I do have some sense that I would rather than say we should be conservative and extrapolate from what we know about this other class of antigen I might say that right now we have insufficient data and cannot make a recommendation.

CHAIRMAN DURST: Dick Durst. Would it be safe to say that for those allergens for which we have sufficient data we would set a realistic threshold based on that; and for those that the data is currently insufficient, that we would use the threshold of the most sensitive?

DR. SILVERSTEIN: That would be safe to do that, but I feel that I could make some judgments with regard to individual patients. I would be cautious about making such a recommendation on a policy basis for that. The consumer might and the industry might want guidance. We may have insufficient data to be able to provide that guidance.

CHAIRMAN DURST: Soheila and then Jean.

DR. MALEKI: Soheila Maleki. Well, I

mean, I agree with you, Marc. I understand your thought, but, again, going back to what the consumer wants, the consumer wants us to err on the side of caution.

I mean, of course that is something that you don't want, to lump everybody in. I a hundred percent agree with you. However, when you hear from the consumers, they would prefer that you err on the side of caution even in the absence of data, which is what it essentially is asking.

In the absence of data to pick the most sensitive food and set a threshold, I think is more comfortable to the consumer or probably would make them feel better than to say nothing on the label at all.

DR. HEIMBURGER: Or, to leave it ambiguous. Doug Heimburger. Or, to leave it ambiguous, to say "It may contain" or whatever.

CHAIRMAN DURST: Jean.

MS. HALLORAN: Yes. I think we should keep in mind that we are talking about a threshold for labeling only. This is not a threshold for

excluding the product or taking it off the market or anything like that. Particularly, the problem comes with what is the threshold for requiring somebody to say, a company to say that "This product contains soy"?

I think to err slightly, perhaps, in the direction of a lower threshold is the appropriate course here until it can be shown that certain very low levels of soy do not pose any hazard to a person with allergies.

Because for most people it is not relevant; it will not be of interest at all. What we are trying to do here is to try to provide information to consumers with a very special concern.

CHAIRMAN DURST: Mark.

DR. NELSON: Yes, Mark Nelson. Earlier, we were talking about gray areas. I think if we went to establishing a threshold based on the most sensitive or the most problematic allergen we would be completely in the black area.

Echoing some of Jean's comments, I think

if we are to establish a threshold based on the most problematic allergen, I can't imagine there would be too many companies that would go through the process of reformulating a product for soy to meet that lower, tight threshold knowing full well that there are data that exist that we are getting close to better information for a higher threshold for soy, and then going back and reformulating again to meet that. In effect, we would be postponing providing useful information to a good portion of the allergic population, if we were to take that tack.

CHAIRMAN DURST: Jeff.

DR. BARACH: Jeff Barach. I would certainly agree with Mark's comments. One thing I would say, though, is that we really from my observation have fairly good data on at least four of the major eight, and that is comforting to me. I wish we had more, but that seems to be what was presented to us.

If we think about what could happen to those other four and we use, say, the lowest level

for the allergen of highest activity, that bothers me a little bit because of what Mark said.

I think what we should recognize, though, is that we do have sort of a default position. Unfortunately, we have a zero tolerance now for those allergens, so those products would be labeled.

It is not like they wouldn't be labeled; it is just that they don't have a threshold. If there is any there, any detectable, then it would have to be labeled. There is a default. We don't have to in my mind assign a threshold for everything at this point and still protect the consumer.

CHAIRMAN DURST: Further discussion?

Ciaran.

DR. KELLY: So is the default threshold an analytical de facto?

DR. BARACH: I would say it is more ingredient-based than analytical.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. When you say

"ingredient-based," so that goes back to "may contain," or what does it mean?

DR. BARACH: It goes back to the system that we are currently using.

DR. BOCEK: Okay. That is the system we are trying to change.

DR. WASLIEN: Don't you mean that you have to list all of the ingredients of a food, so it is not the "may contain"? Is it the list of ingredients? Isn't that what you are referring to? It doesn't mean he is saying we will stick with the "may contain" labeling option. It is if soybean lecithin is added to a food, it is on the list of ingredients.

DR. BARACH: That's right. The "may contain" part covers the possibility of adventitious presence or a contamination during the manufacturing as well. We have the list of ingredients, and then we have the "may contain" for small amounts that may enter the product.

CHAIRMAN DURST: That was Carol and Jeff responding.

Now, Mark.

DR. NELSON: It also covers not only additives and potential cross-contact, but it also includes the processing aids which are intentionally used but really serve no function in the finished product, but there may be trace amounts of it in the product. At this point the law requires us to do it, to label those as well.

DR. TEUBER: Suzanne Teuber. Actually, for those processing aids, many of them will fall under the petitioner notification process.

DR. NELSON: They could.

CHAIRMAN DURST: Any further discussion?

(No response.)

CHAIRMAN DURST: No? We will move on.

DR. TEUBER: Suzanne Teuber going on here. The next part of that question was actually: if so, which food or foods could serve this function; if not, is there a more appropriate method to be used? I think people discussed that here.

The question is, though, do we have a consensus on that for Dr. Durst to write up a

statement? I'm not sure that we do. Do you feel that we do? Because basically this might or might not be an appropriate way to proceed. There were concerns raised for and against. I don't think we had really consensus.

CHAIRMAN DURST: Yes. Well, as I say, I don't think we have to reach a consensus as long as we can provide some guidance to the FDA as far as directions for them to go.

I could ask Steve at this point if he wants any further clarification on that point.

DR. GENDEL: No, you are correct, it is not necessary to reach a consensus but simply stating the range of opinions and the basis for those opinions.

DR. TEUBER: All right.

CHAIRMAN DURST: Okay. Thank you.

DR. TEUBER: Suzanne Teuber. Continuing, number four, the draft report discusses the available data on the levels of protein present in highly refined oils, that is, oil that is hot-solvent extracted, refined, bleached and

deodorized.

Is there any physiologic reason -- for example, food matrix effect denaturation of protein -- why the protein levels in highly refined oils could not be used as the basis for establishing a threshold for other allergenic foods? Are there any other limitations that should be considered in applying this approach to the eight allergenic foods?

With this there was complete consensus that the levels in oils did not apply. The reasons that were raised included the fact that we have extremely poor measurement of proteins in oils. It is very unclear as to their validity.

Secondly, the points raised about denaturation, changing of epitopes and whether the proteins in oils actually reflect what folks really act to.

Then, third, the matrix effect was felt to be extremely important and has been backed up by studies showing that fat can affect the threshold for response.

In addition -- let's see was there yet another, this is where the printer didn't work on that -- we had the configuration changes, we had the measurement problems, and then the matrix. I believe those were the three that we had covered. That one we were in complete consensus agreement on.

CHAIRMAN DURST: Has anyone changed his or her mind on that?

(No response.)

CHAIRMAN DURST: Well, I guess we are still in consensus. Okay, that takes care of those specific questions. Again, I will refer back to Steve, if he has anything that he would like further discussed on the food allergen part?

DR. GENDEL: I don't believe so.

CHAIRMAN DURST: Okay. Then, we can move on to the general questions on the first page of our charge. I think some of these should be able to go fairly quickly, since we have laid all of the groundwork now for it. The first one I will read the questions, and then we can discuss.

"In addition to the four approaches identified by FDA for establishing thresholds (i.e., analytical methods-based, safety assessment-based, risk assessment-based and statutorily-derived) are there other approaches that FDA should consider? If so, please describe and explain why FDA should consider them."

As I recall, there really weren't many other options.

Erica.

DR. BRITTAIN: I just have a really brief comment. It is not really another method, but just that to me the safety assessment-based and the risk-assessment based are sort of part of a continuum.

I don't see them as, necessarily, completely distinct in that I would like to see more statistical principles brought into the safety-assessment-based approach.

CHAIRMAN DURST: Okay. Soheila.

DR. MALEKI: Soheila Maleki. I think I just brought up one method about celiac disease

measurements, and that is, possibility for looking at T-cell activation, which is more likely to catch that amplification of response than analytical methods might. It was just a suggestion, if anybody else has any ideas.

CHAIRMAN DURST: David.

MR. ORYANG: Yes. I would just like to echo that. Yes, the risk-assessment based and the safety-assessment-based methods are really distinct and separate.

However, I think more statistic[s] could be brought into the safety assessment-based such as using distributions within the safety factor or the uncertainty factor, or, for that matter, incorporating uncertainty into the threshold by using a distribution, and then using Monte Carlo simulation to come up with a result, which is a distribution, and then maybe looking at the 95th percentile or whatever values come up from that modeling to set what the ultimate threshold should be.

It is really just adding some aspects of

risk-assessment into, some methods of risk assessment into those factors within the safety-assessment methodology, because there are two dimensions of uncertainty.

If you look at the studies that were done, from what I could see there is, first of all, uncertainty about how closely or how well we capture symptoms or signs. They observe signs. When do the observed signs occur? Should we use the subjective or objective? Because there is a range there as to when the sensitivity is different.

Then, the second part of it is you take this study population, does that study population truly represent the overall population? Can you then take what you have observed here in this study group and project it to the population?

We can't say a hundred percent of the study population represents the other population, so there is uncertainty there. There are really two dimensions of uncertainty as well as, of course, the model that we are using.

There is uncertainty based on the method. There are multiple dimensions of uncertainty. Unless we incorporate some statistic[s] into this, I don't think we are doing a good job. I really suggesting adding some statistic[s] to some of the factors.

CHAIRMAN DURST: Good.

Carol.

DR. WASLIEN: Carol Waslien. I also think I'm not sure if population-based studies of groups exist that are living on gluten-free diets and are included in the risk and safety kinds of categories and studies, because they are not clinical trials.

I think there is some value to be added to looking at population-based evaluations to increase your ability to include highly sensitive, to increase your ability to ask or collect more data on range of responses.

Population-based studies such as that, although they are crude and messy, would give you a better idea of the kinds of ranges of responses that you would see in the free-living population as

opposed to a sample, challenge trial kind of clinical study.

CHAIRMAN DURST: Well, Marc and then David.

DR. SILVERSTEIN: I don't have a suggestion for another approach. However, within the approach, I was struck by the choice of a 10 percent proportion, a population that would respond to a milk allergy in an identification of a hypoallergenic formula to derive a buff sample size of about 29 subjects using a conventional 95-percent confidence interval to identify a proportion or a rate of 10 percent as a basis for what has become an accepted sample size for these sorts of studies.

Indeed, it is difficult to do the studies. They are expensive; they are risky; and it takes time to recruit subjects. These conditions perhaps are not very common; so, referral in the collection of an adequate number of patients means that, by and large, investigators are performing studies of about that size.

We have a collection of literature which is maybe sufficient for one purpose but may not be sufficient to make estimates of thresholds. Estimates of thresholds are not estimates of a certainty about an incidence rate of 10 percent, but it is a measurement of a quantity around which we can decide the amount of precision needed, and then derive sample size estimates.

Now, indeed, when those sample size estimates begin to be large, we have to face the challenge of how do we do those studies. Do they require multicenter studies? Do they require longer periods and more effort to recruit? Do they require larger budgets?

These are real factors. In the real world, of course, we must live with the available data and the available resources as we collect information. I do think there is an important distinction between the sample needed to estimate with fairly reasonable or conventional confidence a rate of 10 percent and the sample needed to make estimates of thresholds.

Depending on how precise your estimates could be, your samples might be about that size or they might be much larger. There should be more conscious decision making in setting the size of those samples as well as thinking about the thresholds themselves.

CHAIRMAN DURST: David and then Erica.

MR. ORYANG: Yes, David Oryang. Further about some of the methodologies, a lot of times if the resources are available, time being one resource, and the need is there to really go do a more in-depth analysis, then the risk-assessment-based approach, looking at dose response and exposures, would be the method to go, but the data is not currently available.

I will just suggest that sometimes if one does take the risk-assessment-based approach, you can still do it, but there would be a lot of uncertainty in a lot of the parameters.

To the extent that they can be transparently presented, maybe it is still viable. I haven't really seen the evidence that we have

enough on some of the dose responses and exposures.

I know that in this report there is enough stated in there, and it is suggested that the risk-assessment-based approach be the preferred approach for the allergens but not for the glutens.

Maybe that is also because of the acute nature of the allergens. I mean, the consequence of not looking further into it seems to be more acute than in the gluten case.

I concur with FDA in some of these recommendations. I would just say that if the resources are available and more information is available, the risk-assessment-based approach is the better approach.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Yes, I really want to echo what Marc said. This magical sample size of 29 that we kept hearing I really think is not quite, even if you want to just exclude a 10 percent rate, which doesn't seem like really enough for the threshold setting, it is not set up the way I think people would normally want to set things up to have

appropriate statistical power. That is one relatively minor point.

It all goes back to what I said originally that I think you need to set a precise goal of how much risk is acceptable, and that will drive the sample size. If that sample size is way beyond what can be done, then I think you have to go to the modeling approach with the right data.

CHAIRMAN DURST: Further discussion? Ciaran.

DR. KELLY: Ciaran Kelly. I just wanted to reinforce the comment that has already been made of the value of including population experiences within the safety assessment.

Unfortunately, not only is there a wealth of experience, but there are also a number of publications that document the efficacy in a population of certain levels of gluten exposure.

I think that if one were to consider the more conservative thresholds that are currently in use, there would be the likelihood that those thresholds would be dangerous as opposed to safe

would seem to be very low.

CHAIRMAN DURST: Mark.

DR. NELSON: Yes, Mark Nelson. I wanted to come back to comments that Marc and Erica made, but maybe emphasize it a little differently. I fully agree with basing this all on science and having statistical rigor, but we also have to make sure we are not having to prove we're the enemy or the good.

We may need to adjust the studies for different allergens, for example, depending on the severity of the response, and so on.

We shouldn't forget that the sample size used to support the hypoallergenic infant formula was also for a population whose sole source of nutrition was the infant formula that they were taking in. I mean, safety was clearly considered in that situation, and, again, it serves the greater portion of that population.

CHAIRMAN DURST: Any further discussion?

(No response.)

CHAIRMAN DURST: We are ready to move on

to the second question. I will read it again:

"Are FDA's criteria for selecting and evaluating the available data appropriate? If not, should any of the criteria be modified or deleted? Please describe any changes you would like to see and why. Are there additional criteria FDA should consider?"

Who would like to start that off?

DR. BRITTAIN: I think we have already covered all of this. I don't know if there is anything else?

CHAIRMAN DURST: Yes, I don't know if there are any more.

Marc.

DR. SILVERSTEIN: Mark Silverstein. There was a very useful document prepared and funded by the Agency for Healthcare Research and Quality. I mentioned it yesterday, and it was "Methods for Evaluating the Strength of Evidence." It was I think prepared by one of the evidence-based practice centers under contract from the Agency for Healthcare Research and Quality. It has been

published, and it is available on their Web site. It basically summarizes a set of methodologic criteria that you would use in doing, evaluating, grain- or mice-controlled trials, cohort studies, studies or diagnostic tests.

In looking through the list of the criteria that are in the FDA report, almost all of the criteria are mentioned, maybe not in exactly the same format as in that publication. It seems to me, that since it is our taxpayer dollars at work and other agencies have already developed this, it would be useful to look at it.

I do believe the diagnostic test section, which would be relevant for some of the food challenges, has a different way of phrasing some of the focus on the selection of the patients.

I do think it would be a useful resource both to cite and perhaps to look at to see that the categories suggested by that thoughtful review are well covered in all of the categories.

CHAIRMAN DURST: Okay. Ciaran and then Erica.

DR. KELLY: Ciaran Kelly. Yes, I have just one comment, and it has to do with the criteria for evaluating analytic methods. To my mind, transparency of the method, an adequate description of the specific methodology, would be important so that potential biases or weaknesses that are inherent within the methodology could be examined in addition to the other criteria that you list.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I just have a very brief comment. In terms of beefing up the summary of studies in the appendix, maybe along the lines that Marc suggested, one thing that is not in there is number of patients in each study. That seems like a critical omission.

CHAIRMAN DURST: Anything else?

Jean.

MS. HALLORAN: Jean Halloran. I was intrigued by the suggestion from Dr. Taylor who mentioned that clinicians have data on NOAELs and LOAELs for their patients in their records. This

is certainly not data which is a placebo-controlled, double-blind study; it is not peer reviewed; and it is not many other things.

Given that there seems to be such a dirth of data, especially for certain allergens, I am wondering whether any effort could be made or whether there would be any value to FDA asking for such data just to somehow get a vague idea of what is going on in those areas, whether it is possible to do that, or whether once data is submitted, it gets a life of its own and it is more trouble than it's worth?

CHAIRMAN DURST: Okay. That actually leads us into the third question.

DR. BRITTAIN: Well, I mean, it relates to this, which is that my concern about that is that if those studies were done almost exclusively on patients for whom they were trying to confirm a diagnosis, they would be really biased.

Even if there is a large number of them, if the information came from it is really biased and is wrong, then it doesn't really help that you

have a lot of data.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. Just one comment. The studies that they used for a challenge, and I think Suzanne can confirm that, is the doses that are used are often much higher than threshold doses. Actually, if you use that data, you would be targeting people that have really high threshold doses, if they didn't react at that level.

CHAIRMAN DURST: Margaret.

DR. McBRIDE: I think, though, that those concerns about that kind of data could be handled by only including subjects who responded. Obviously, you don't want subjects that didn't respond, because you don't even know if they are sensitive. There are ways still of looking at that data and possibly having something.

CHAIRMAN DURST: Suzanne.

DR. TEUBER: Suzanne Teuber. That data, it actually would be very useful to have if we are trying to start characterizing subpopulations of

patients. Because we know that the vast majority of patients where there is likely this NOAEL data that just wasn't published are patients who are children with atopic dermatitis.

That is a distinct subgroup with usually not as severe a reaction, and so it might be very useful to have that, because we still need more data. We can help characterize more, then.

CHAIRMAN DURST: Since we are dealing with question three, let me just read it into the record.

(Laughter.)

CHAIRMAN DURST: "Recognizing that some of the key studies (i.e., challenge studies) are ongoing, what if any use of preliminary data that have not been peer reviewed for establishing thresholds is appropriate?"

Now we can continue.

David, did you have your hand up?

MR. ORYANG: Yes, I did have my hand up. Just briefly, about the data. I don't see very much put in there about expert opinion and clear

methods of being able to elicit some of this kind of information that is kept in records, and so forth, from a panel of experts and clearly documented in a way that can be presented scientifically in the document to be included as part of the record in how the decision came to be.

I think it would be useful if there was a formal process for getting that kind of information from doctors and other people who can be considered experts on those specific areas, elicit that information formally and document it, and then show a clear method of how you came from the broad opinion to the narrowed result or determination that was made.

I think that is also a good process of getting that kind of unpublished or informal information which can be looked at as a knowledge, which is important in decision making.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. Again, I mean, of course any data that any scientist is beautiful and wonderful to get. But, again, I

don't think that in establishing thresholds, which is what we are looking at, that the challenge studies would be.

Again, it is wonderful, yes, if we were going to divide people into subpopulations. Bottom line, we are looking at the most severe reactions, which I don't think will be included in that data because of the high doses of the challenge, or often higher doses.

DR. BRITTAIN: And the populations that would undergo those challenges.

DR. MALEKI: Yes. Essentially for this, yes. I mean, of course it is wonderful to have the data. What scientist or doctor or agency doesn't want more data? But bottom line that is --

CHAIRMAN DURST: Suzanne.

DR. TEUBER: Suzanne Teuber. Just to address Mr. Oryang's comments, actually the First Threshold Conference that was held, the paper by Steve Taylor and all, that was bringing together people who had unpublished data about thresholds, and from there it has gone on to the current

consensus protocol.

The data that was referred to by Dr. Taylor was something that was brought to the table, but again it was this population that was more atopic dermatitis. I still think it would be interesting to have it. It would cost money to get it, to pay somebody.

However, it is true it would not give information directly related to the safety-assessment threshold information we want. It is just population data that is of interest.

CHAIRMAN DURST: Mark.

DR. NELSON: Mark Nelson. I guess I would echo Jean's comment and a lot of other people, to try to get more data. What I understood Steve Taylor to describe, the specific example he gave, was Hugh Sampson's work.

This is the extra data from a peer-reviewed study, which strikes me, hearing the clinicians speak and others, that this would be very useful for helping specify the uncertainty factors we have talked about and also help us maybe

with some of these subjective responses. I don't know, I haven't seen the data.

CHAIRMAN DURST: Jeff.

DR. BARACH: Jeff Barach. As we heard, other countries are struggling with the issues of allergens also. I would just make note that the European Food Safety Authority and the European Commission have put together a Directive 2005/26/EC.

I would encourage the FDA to contact the European Food Safety Authority to find out if they have any data that would be of interest to our group as they work on the issue.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. I think that is a really good point, and I also think Health Canada, but I think they have already talked to them about it. That is a very good point.

CHAIRMAN DURST: Margaret.

DR. McBRIDE: I understand the concern about the difference, the potential difference, in dosing for challenge tests versus threshold

testing. We have already established that if there is a LOAEL in the absence of a NOAEL, that is not very useful.

On the other hand, if within that data there are individuals that prove to be sensitive to whatever is being test and the NOAEL is available as well as the LOAEL, that is clearly relevant data.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. Just a quick comment to that. Yes, it is very valuable, but it has to be done with the right population. If that was a patient where it was a diagnostic challenge, a question of biology, it is not as valuable as somebody who has a clear-cut clinical presentation of anaphylaxis to a food allergen. Yes, that is the right person to look for a threshold.

CHAIRMAN DURST: Any further discussion?

Ciaran.

DR. KELLY: Ciaran Kelly. I just wanted to perhaps more directly address the question about non-peer-reviewed experimentation. Clearly, the

presentation that Dr. Fasano gave to us yesterday is not peer reviewed and published, but, nonetheless, it is directly pertinent and relevant to the question at hand and also is performed by a well-recognized, expert group of investigators.

Clearly, that is a double-blind, randomized-controlled trial. Clearly, those data are highly relevant. Although it is likely that they will be published within the next year, that publication process is sometimes very hard to predict, and it could be much longer than a year. I would feel personally, and I don't know if the rest of the Committee agrees, that those data are highly relevant.

CHAIRMAN DURST: Any further discussion?

(No response.)

CHAIRMAN DURST: Before we wrap things up, I would also like to ask does anyone have any specific comments on anything in the report, anything that jumped out at them that needs some modification or correction?

Yes, Ciaran.

DR. KELLY: Ciaran Kelly. I do have some minor suggestions, but I don't want to take up the Committee's time with it. What is the mechanism? Should I submit some --

MRS. MOORE: He has asked the question, so go ahead. Go ahead.

CHAIRMAN DURST: I mean, is it proper just to provide that to the Working Group?

DR. KELLY: I don't want to waste the Committee's time with very, very minor things.

MRS. MOORE: Okay. You can send it to me.

DR. KELLY: I can provide that in the form of a memo.

MRS. MOORE: Okay.

CHAIRMAN DURST: Again, I want to refer back to Steve. Any specific questions that you might have before we wind things up here?

DR. GENDEL: (Off microphone.) Yes, I just want to remind everyone that there is a mechanism for submitting information through the docket. You can access that through the FDA homepage. Any information that is relevant can be

put in there.

MRS. MOORE: Steve, start from the top because you weren't heard from the beginning of your statement.

DR. GENDEL: Okay. This is Steve Gendel. The response was that any information can be submitted through the docket, which is available. Any relevant information can be submitted through the docket available through the FDA homepage.

CHAIRMAN DURST: Okay. I think we are at the point now that I can ask Mr. Landa to make some closing comments.

Closing Comments

MR. LANDA: Thank you, Dr. Durst. I will be very brief. First, I just want to reiterate Dr. Brackett's thanks to all of the members of the Committee for lending us your expertise for these several days. We rely heavily on experts from outside as well as within the Agency. Of course, this is one of the principle ways in which we obtain outside expertise.

The second point, just in case not

everyone heard it, the point Steve Gendel made. The docket will remain open for another several weeks until the middle of August. Anyone who has comments on the report please get them to us through the docket.

We will consider any comments from the public as well as the results and the comments, sort of consensus statements, from this meeting in making any changes to the draft report and in taking our next steps after the draft report is finalized.

The last thing is I would just like to reiterate the thanks noted earlier to Marcia Moore and her colleagues for putting on the meeting. Thank you.

MRS. MOORE: Thank you.

CHAIRMAN DURST: Thank you.

I believe Marcia said the transcript of this meeting would be available at the end of August?

MRS. MOORE: Yes.

CHAIRMAN DURST: Without any further

comments, I will declare this meeting adjourned.

Thank you very much everyone.

(Whereupon, at 9:37 a.m., the meeting was adjourned.)